CHRD 2021: Abstract & Poster Submission Form

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Research Category:

- ◉ Basic Science
- ○ Clinical
- ○ Community Health / Policy

What was your role in the project?

- ☑ Design
- ☑ Perform Experiments
- ☑ Analyze Data
- ☑ Write Abstract
- ☐

Presenter Status:

- ○ Undergraduate Students
- ◉ Masters Student
- ○ PhD Student
- ○ Post-Doctoral Fellows
- ○ Residents
- ○ Non-Trainee

Title

Identifying Potential Otoprotectants For the Prevention of Cisplatin-induced Ototoxicity in Pediatric Patients

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Background

Cisplatin is highly effective in the treatment of many different cancers. One of the most common adverse drug reactions (ADR) associated with cisplatin is ototoxicity (hearing loss). This ADR occurs in up to 80% of oncology patients, with pediatric patients at a five-fold higher risk for experiencing hearing loss after treatment with cisplatin.

Objective

As this ADR has been shown to be heritable, we aimed to use genomics-driven drug repurposing analyses to identify otoprotectants for the prevention of cisplatin-induced ototoxicity (CIO).

Methods

A transcriptome-wide association study (TWAS) was performed to investigate the association between imputed gene expression and hearing loss, using genomic data generated from four heritable hearing traits from the UK Biobank. Genes that were associated with hearing loss ($p<0.05$; 90%-credible) were filtered based on whether their expression was correlated with cisplatin-induced cytotoxicity ($p<0.05$) and if they were expressed in the inner ear. Finally, drug repurposing analyses were performed to identify small molecules with highly dissimilar gene expression profiles to those associated with hearing loss, which may be prioritized as otoprotectants.

Results

TWAS and fine-mapping analyses identified 178 genes that were associated with hearing traits. After filtering for correlation with gene expression and cisplatin cytotoxicity, 60 genes remained. Of these, 54 genes were found to be expressed in the inner ear. Drug repurposing analyses revealed that the top scoring perturbagen gene expression profiles were involved in various hearing related pathways.

Conclusion

Drug repurposing analyses, based on TWAS gene results, led to the identification of candidate otoprotectants. Hearing difficulties have a dramatic impact on the educational and social performance of children due to underdeveloped language skills. Results from this study are of utmost importance as the identification of otoprotectants will help reduce the burden of CIO in pediatric cancer patients.

Authors

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